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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/148,234	09/04/1998	IOANNIS MOUTSATSOS	GI5298A	3002

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EXAMINER	
SANDALS, WILLIAM O	
ART UNIT	PAPER NUMBER
1636	25

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/148,234	Applicant(s) Moutsatos et al.
	Examiner William Sandals	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 20, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11, 12, 14-17, and 19-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11, 12, 14-17, and 19-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8 & 24*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Amendments to the specification in Paper No. 23, filed November 21, 2001 have overcome the objection to the specification in the previous office action, and the objection is withdrawn. The substitute specification has been entered.

2. Amendments to claim 15 in Paper No. 23 have overcome the objection to the claim in the previous office action, and the objection is withdrawn.

3. The arguments presented in Paper No. 23 regarding the rejection of the claims under 35 USC 103 are not found convincing and the rejection is repeated below along with responses to the arguments.

Response to Amendment

4. The declaration of Debra Pittman under 37 CFR 1.132 filed in Paper No. 23 is insufficient to overcome the rejection of claims 11, 12, 14-17 and 19-23 based upon USC 103 as set forth in the last Office action because: The methods of the declaration do not specifically relate to the methods of the claimed invention. The claimed invention is directed to a method of transfecting bone marrow progenitor cells *in vitro* with BMP-2 for the production of cells for implantation. The experiments of the instant declaration are directed to the injection of DNA encoding BMP-2, compared to the injection of DNA encoding BMP-10 into an animal. The

results of the experiments provided in the declaration do not exemplify nor expand on the teachings of the specification as it applies to the claimed invention. The results of the experiments of the declaration demonstrate that *in vivo* injection and subsequent expression of BMP-2 produces different results when compared to *in vivo* injection and subsequent expression of BMP-10. The two growth factors being different, this result is expected. The instant rejection discusses the interchangeability of BMP-2 with BMP-10 for the purpose of inducing differentiation and proliferation of transfected bone marrow progenitor cells. The declaration of Debra Pittman does not address this issue, and as such, does not provide any convincing data to show that BMP-2 and BMP-10 are not interchangeable in the context of the claimed invention. In addition, the data do not convince of unexpected results since the experiments do not use protocols which are comparable to the claimed invention, and the results of the experiments of the declaration have little information to impart for relevant comparison, other than re-establishing the already well-known fact that BMP-2 and BMP-10 are different and consequently can be expected to have different properties. The use of BMP-2 and BMP-10 as inducers of proliferation and differentiation are the points at issue, not that they may possess different biological or physical properties, which, by definition, they do because they are, in fact, different proteins.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 11, 12, 14-17, and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,763,416 (of record) or WO 96/39431 (of record) in view of US Pat No. 5,645,084 (of record), US Pat No. 5,700,774 (of record) and US 6,048,964.

US Pat No. 5,763,416 taught (see especially columns 3-5 and 7-12) or WO 96/39431 taught (see especially pages 2, 15-16, 19, 33 and the claims) a method of producing cultured or bone marrow stromal cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein. US Pat No. 5,763,416 at column 3 suggests the use of PTH in the method, where BMP and PTH can be coexpressed in the target cells, and identifies the requirement of BMP and/or PTH receptors in the target cells. US Pat No. 5,763,416 at column 4 suggests the use of bone progenitor cells. WO 96/39431 taught that the bone morphogenic protein was BMP-10. US Pat No. 5,763,416 taught that the method may be practiced with BMP-2 as well as other bone morphogenetic proteins.

US Pat No. 5,763,416 did not teach that the cells coexpress PTH and a PTH receptor. WO 96/39431 did not teach that the BMP was BMP-2, nor that the cells were progenitor cells, nor that the cells coexpress PTH and a PTH receptor.

US Pat No. 5,645,084 taught (see especially column 4) that BMP-2 is closely related to the BMP-10 of WO 96/39431, where BMP-2 and BMP-10 may be used interchangeably in a method of use for treating a bone infirmity.

US Pat No. 5,700,774 taught (see especially columns 1 and 2) the interchangeability of BMP-2 and BMP-10, as well as the use of PTH and PTH receptor in cells in need of treatment with BMP-2, where the affected bone-generating target cells are known to express PTH receptor.

US 6,048,964 (see especially the abstract, summary and columns 5-8) taught that recombinant DNA sequences were used to produce the BMP-2 protein in cells, and that BMP-2 was known to produce differentiation and proliferation of bone progenitor cells.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant specification to combine the method of producing cultured or bone marrow progenitor cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of US Pat No. 5,763,416, or the method of producing cultured cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of WO 96/39431 with the interchangeable BMP-2 protein of US Pat No. 5,645,084 or the interchangeable BMP-2 protein of US Pat No. 5,700,774 where PTH and PTH receptor are known to be produced in the target cells of the method because all of the references taught the treatment of bone infirmities with BMP's, and the BMP's are shown to be interchangeable for the use of treating a bone infirmity, and PTH and PTH receptor are known to be expressed in the target cells.

One of ordinary skill in the art would have been motivated at the time of filing of the instant specification to combine the method of producing cultured or bone marrow progenitor cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of US Pat No. 5,763,416, where US Pat No. 5,763,416 recites at column 4, "this invention provides advantageous methods for using genes to stimulate bone progenitor cells" or the method of producing cultured cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of WO 96/39431 which recites at page 19 "cells from a patient may be engineered with a polynucleotide (DNA or RNA) encoding a polypeptide *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide", with the interchangeable BMP-2 protein of US Pat No. 5,645,084 or the interchangeable BMP-2 protein of US Pat No. 5,700,774 because all of the references taught the advantageous use of BMPs for treatment of bone infirmities by stimulating progenitor cells to proliferate. BMP-2 was taught to be produced recombinantly and to produce proliferation and differentiation in bone progenitor cells in US Pat No. 5,645,084. US Pat No. 5,645,084 also taught that BMP's are shown to be interchangeable for the use of treating a bone infirmity. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US Pat No. 5,763,416 or WO 96/39431 with US Pat No. 5,645,084 and US Pat No. 5,700,774.

Response to Arguments

7. Arguments set forth in Paper No. 15 assert that the amendment in Paper No. 15 to claim 11 has avoided the rejection of the claims over WO 96/39431 since the claims are now drawn to BMP-2 and WO 96/39431 teaches BMP-10. This is not found convincing since the obviousness of the teachings of WO 96/39431 are still relevant given the teachings of US Pat No. 5,763,416, US Pat No. 5,645,084 and US Pat No. 5,700,774. WO 96/39431 teaches the use of a BMP protein which has been produced by recombinant means used in a method of treatment of a bone deformity by acting on bone progenitor cells to proliferate and differentiate.

8. Arguments set forth in Paper No. 15 assert that apoptosis appeared to be less in cells transfected with an adenovirus vector encoding BMP-2. The reduction is apoptosis which is taught in the specification at page 47 teaches that apoptosis "decreases with time". This is a logically expected result of the induction of proliferation and differentiation. A reduction in apoptosis is an expected result of induction of proliferation and differentiation.

9. Arguments set forth in Paper No. 15 assert that the addition of BMP-2 to cells produced a "positive effect on differentiation and proliferation". This is expected, given the teachings of the prior art in the rejection above that BMP-2 produces proliferation and differentiation.

10. Arguments set forth in Paper No. 15 assert that the instant invention presents "unexpectedly improved results over the prior art BMP expression systems". This is not found convincing, since BMP's of the prior art of the above rejection also taught an increase of proliferation and differentiation. No showing of unexpected results is found in the specification over these teachings.

11. Arguments set forth in Paper No. 23 assert that the claims are distinct over the prior art because BMP-2 causes less apoptosis than BMP-10. This is not a claim limitation, and as such the point is moot. As far as providing unexpected results, the reduction of apoptosis as noted in the specification occurred in the test sample which was undergoing differentiation and proliferation (see page 46 lines 12-19 of the newly submitted substitute specification), where it is speculated that this reduction in apoptosis occurred as a result of the differentiation process.

It would be a natural consequence of cells undergoing proliferation to have reduced apoptosis. This point is addressed in US 6,048,964 at column 5, lines 29-50 where it states that cells undergoing differentiation are expected to also undergo changes in gene expression patterns relative to the progenitor cell. Changes in expression, morphology and cell physiology can be used to monitor the effect of a bone morphogenic protein on a differentiating and proliferating cell. This teaching is directed to the well known fact that a change in expression patterns is commonly associated with a reduction in apoptosis in differentiating and proliferating cells.

12. The publication by Moutsatsos et al. in Molecular Therapy, volume 3:449-461 is asserted to teach nonobviousness of the instant invention. The above mentioned article does not teach any unexpected results over any of the well known BMP proteins. No points are raised in Paper No. 23 where this reference may provide a basis for non-obviousness.

13. Arguments set forth in Paper No. 23 assert that the methods of the prior art are at best suggestions of "obvious to try" methods. US 5,700,774 taught the use of BMP-2 protein to induce proliferation and differentiation of progenitor cells in a method of treating bone

deformities and bone growth by inducing the development of new bone and cartilage cells in a site of treatment. Therefore, it was an established and well known fact that BMP-2 caused proliferation and differentiation of bone progenitor cells in a method of treatment of bone deformities and bone growth. US 5,763,416 taught the treatment of bone deformities and bone growth by transfecting bone progenitor cells with a BMP protein. BMP-2 is stated to be a known BMP protein which will induce bone progenitor cells to undergo proliferation and differentiation. Ex-vivo transfection of the bone progenitor cells is discussed at column 5, lines 1-49. Therefore, it is obvious to combine the teachings of US 5,763,416 and US 5,700,774 to produce the invention of transfecting bone progenitor cells with a gene expressing BMP-2 to produce cells which would be used in a method of treating bone deformities and bone growth.

14. It is further asserted that the use of BMP-2 obtained unexpectedly improved results over the use of BMP-10. No showing of this claim has been provided.

Conclusion

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
February 1, 2002

TERRY MCKELVEY
PRIMARY EXAMINER